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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES**

Application of: Rein *et al.*

Confirmation No.: 8812

Serial No.: 09/980,727

Group Art Unit: 1618

Filed: July 8, 2002

Examiner: Rogers, James William

For: METHOD FOR PRODUCING A WATER-
INSOLUBLE AMORPHOUS OR PARTIALLY
AMORPHOUS CONTROLLED-RELEASE MATRIX

Attorney Docket No.: 11390-009

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

**JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939
Attorneys/Agents for Appellant**

TABLE OF CONTENTS

	<u>PAGE</u>
I. REAL PARTY IN INTEREST	1
II. RELATED APPEALS AND INTERFERENCES	2
III. STATUS OF CLAIMS	2
IV. STATUS OF AMENDMENTS	3
V. SUMMARY OF CLAIMED SUBJECT MATTER	3
VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL	4
VII. ARGUMENT	4
A. THE APPLICABLE CASE LAW, REGULATIONS AND GUIDELINES	4
B. THE REJECTIONS UNDER 35 U.S.C. § 102(B) AND 35 U.S.C. § 103(A) OF CLAIMS 1, 5, 6, 10, 16-18 AND 20-32 SHOULD BE REVERSED	6
1. THE REJECTION OF CLAIMS 10, 16-18 AND 23-32 UNDER 35 U.S.C. § 102(B) AS ANTICIPATED BY EUROPEAN PATENT APPLICATION NO. 580 860 A1 TO NAKAMICHI <i>ET AL.</i> (“NAKAMICHI”) SHOULD BE REVERSED	6
2. THE REJECTION OF CLAIMS 10, 16-17 AND 23-32 UNDER 35 U.S.C. § 102(B) AS ANTICIPATED BY INTERNATIONAL PATENT PUBLICATION NO WO 92/15285 TO LENTZ <i>ET AL.</i> (“LENTZ”) SHOULD BE REVERSED SHOULD BE REVERSED	8
3. THE REJECTION OF CLAIMS 1, 5-6, 10, 16-18 AND 20-32 UNDER 35 U.S.C. § 103(A) AS OBVIOUS OVER EUROPEAN PATENT APPLICATION NO. 580 860 A1 TO NAKAMICHI <i>ET AL.</i> (“NAKAMICHI”) SHOULD BE REVERSED	9
4. THE REJECTION OF CLAIMS 1, 5-6, 10, 16-18 AND 20-32 UNDER 35 U.S.C. § 103(A) AS OBVIOUS OVER INTERNATIONAL PATENT PUBLICATION NO WO 92/15285 TO LENTZ <i>ET AL.</i> (“LENTZ”) SHOULD BE REVERSED	11
5. SUMMARY	16
VIII. CLAIMS APPENDIX	16
X. EVIDENCE APPENDIX	16
XI. RELATED PROCEEDINGS APPENDIX	16

TABLE OF AUTHORITIES
FEDERAL CASES

Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631 (Fed. Cir. 1987)4

Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003)...4

Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999).....4

Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565,
1576 (Fed. Cir. 1991).....4

Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236 (Fed. Cir. 1989).....4

KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d
1385 (2007)..... 4, 5, 6, 9, 10

Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966).....5

In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).....5, 15, 16

Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.,
520 F.3d 1358, 1364-65 (Fed. Cir. 2008).....6

In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007).....6

Abbott Laboratories v. Sandoz, Inc., 529 F.Supp.2d 893, 916 (N.D. Ill 2007).....6

Interconnect Planning Corp. v. Feil, 774 F.2d 1132 (Fed. Cir. 1985)6

In re Wesslau, 353 F.2d 238, 241 (C.C.P.A. 1965).....6, 7

Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565 (Fed. Cir. 1985)7

Structural Rubber Prod. Co. v. Park Rubber Co., 749 F.2d 707 (Fed. Cir. 1984).....7

In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).....9

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)..... 10

In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991)..... 15

FEDERAL STATUTES AND REGULATIONS

35 U.S.C. § 102 4, 6, 8, 10, 17

35 U.S.C. § 103 4, 6, 9, 11, 17

35 U.S.C. § 134 1

XII. CONCLUSION	17
XIII. CLAIMS APPENDIX	18

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APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal under 35 U.S.C. § 134 from a final rejection mailed October 19, 2009 of claims 1, 5, 6, 10, 16-18 and 20-32 of the above-identified application. The Notice of Appeal accompanied by a Pre-Appeal Brief Conference Request was filed on March 18, 2010. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on April 29, 2010. Appellants submit this original appeal brief accompanied by (i) a Petition to Extend Time for Filing a Brief on Appeal for five (5) months from May 29, 2010 to and including October 29, 2010; and (ii) a Brief on Appeal Fee Transmittal Sheet.

I. REAL PARTY IN INTEREST

EURO-CELTIQUE, S.A. is the real party of interest. EURO-CELTIQUE, S.A. is the assignee of the right, title, and interest of inventors Hubert Rein and Klaus-Jurgen Steffans, which assignment was recorded with the U.S. Patent and Trademark Office on May 29, 2002 and recorded on Reel 012932, Frame 0274.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any other pending appeals or interferences relating to the above-identified application.

III. STATUS OF CLAIMS

Claims 1, 5, 6, 10, 16-18 and 20-32 have been finally rejected in the final Office Action mailed October 19, 2009, which final rejection was maintained by a Notice of Panel Decision from Pre-Appeal Brief Review mailed April 29, 2010. The rejections of claims 1, 5, 6, 10, 16-18 and 20-32 are being appealed. Claims 2-4, 7-9, 11-15 and 19 are canceled

The present application was filed as a national stage application under 35 U.S.C. § 371 on October 19, 2001 with claims 1-19. The present application is a national stage application of International Application No. PCT/EP/00/03612 filed April 20, 2000, which published as International Patent Application Publication No. WO 00/64415 on November 2, 2000. The present application claims priority benefit of German Patent Application No. 199 18 325.2 filed April 22, 1999.

In a Preliminary Amendment filed on October 19, 2001, claims 3-9 and 12-19 were amended. Claims 1-4, 6 and 10 were amended, claims 7-9, 11-15 and 19 were canceled, and claims 20-32 were added in the Reply under 37 C.F.R. § 1.111 with Amendment filed on March 11, 2005 in response to an Office Action mailed on February 11, 2004. Claims 1, 4 and 10 were amended, and claims 2 and 3 were canceled in the Reply under 37 C.F.R. § 1.111 with Amendment filed on October 4, 2005 in response to an Office Action mailed on April 5, 2005. A Final Office Action mailed on January 11, 2006 finally rejecting claims 1, 4-6, 10, 16-18 and 20-32. A response to the January 11, 2006 Final Office Action, along with a Request for Continued Examination and a Declaration of Dr. Hubert Rein under 37 C.F.R. § 1.132, was filed on February 12, 2007, wherein no amendments to the claims were made.

Another non-final Office Action was mailed on May 11, 2007, a response to which was filed on November 12, 2007, in which no amendments to the claims were made. A subsequent Final Office Action was mailed on April 22, 2008, a response to which, along with a Request for Continued Examination, was filed on October 22, 2008, in which claims 1 and 10 were amended, and claim 4 was canceled. Another non-final Office Action was mailed on January 14, 2009, a response to which was mailed on July 14, 2009, in which no amendments to the claims were made.

A Final Office Action was mailed on October 19, 2009. A Notice of Appeal and a Pre-Appeal Brief Conference Request were filed on March 18, 2010. The final rejections were maintained by a Notice of Panel Decision from Pre-Appeal Brief Review mailed April 29, 2010.

A full listing of the claims is in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

Appellants filed no claim amendments after the October 19, 2009 mailing date of the Final Office Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The pending claims relate to controlled release matrices, and to methods for producing a controlled release matrices. In one aspect, the pending claims are directed to methods of producing controlled release matrices, wherein the method comprises co-extruding through an extruder a composition comprising a dry mixture of at least one pharmaceutically active agent and at least one starch, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure, and wherein the co-extruding is under sheer force, temperature and pressure conditions such that the starch in the extruded controlled release matrix is vitrified, and wherein up to 15% by weight water is added to the composition prior to co-extruding. This aspect is embodied by independent claim 1. Support in the specification for independent claim 1 is found on page 3, lines 9-15; page 4, line 26 to page 6, line 23. In another aspect, the pending claims are directed to controlled release matrices produced by the claimed methods. This aspect is embodied by independent claim 10. Support in the specification for independent claim 1 is found in the specification at page 3, lines 9-15; page 4, line 21 to page 6, line 23; page 6, lines 25-28; and page 9, lines 26-28.

In another aspect, the pending claims are directed to a controlled release matrix, comprising at least one starch and at least one pharmaceutically active agent, wherein the starch in the matrix is vitrified, and wherein the starch and pharmaceutically active agent were co -extruded. This aspect is embodied by independent claim 25. Support in the specification for independent claim 25 is found at page 3, lines 9-26; page 4, lines 4-5; and page 4, line 26 to page 5, line 18. In particular aspects, the matrix is free of pores, or is water-insoluble.

VI. GROUNDS OF REJECTIONS TO BE REVIEWED ON APPEAL

The following grounds of rejection are presented for review in this appeal:

Whether claims 10, 16-18 and 23-32 are anticipated under 35 U.S.C. § 102(b) by European Patent Application No. 580 860 A1 to Nakamichi *et al.* (“Nakamichi”).

Whether claims 10, 16-17 and 23-32 are anticipated under 35 U.S.C. § 102(b) by International Patent Publication No WO 92/15285 to Lentz *et al.* (“Lentz”).

Whether claims 1, 5, 6, 10, 16-18, and 20-32 are obvious under 35 U.S.C. § 103(a) over European Patent Application No. 580 860 A1 to Nakamichi *et al.* (“Nakamichi”).

Whether claims 1, 5, 6, 10, 16-18, and 20-32 are obvious under 35 U.S.C. § 103(a) over International Patent Publication No WO 92/15285 to Lentz *et al.* (“Lentz”).

VII. ARGUMENT

The rejections of claims 1, 5, 6, 10, 16-18 and 20-23 should be reversed on the grounds that neither of the cited references either anticipates or renders obvious the claimed subject matter.

A. Applicable Case Law, Regulations and Guidelines

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). *See also, Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) (stating that the “identical invention must be shown in as complete detail as is contained in the patent claim”).

A finding of obviousness requires that “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d

1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the “teaching, suggestion, or motivation” test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the Supreme Court affirmed that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant’s disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 USPQ at 1397:

A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into the use of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* -- which are still good law post-*KSR* -- require that *both* the suggestion and the expectation of success must be found in the prior art, and not from knowledge gained from the applicant’s disclosure.

Moreover, a recent post-KSR Federal Circuit decision explained that a non-rigid “flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis” and assures that the obviousness test proceeds on the basis of evidence that arise before the time of invention as the statute requires. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (citing *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Furthermore, in an obviousness inquiry, “every claim limitation of the invention at issue must be found to exist in the prior art references.” *Abbott Laboratories v. Sandoz, Inc.*, 529 F.Supp.2d 893, 916 (N.D. Ill 2007).

The case law further requires that each reference must be evaluated as a whole, *i.e.*, disclosures in the reference that diverge from and teach away from the invention cannot be disregarded. “Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time--a technician without our knowledge of the solution.” *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). “It is impermissible within the framework of a Section 103 rejection to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art.” *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

B. The Rejections Under 35 U.S.C. §§ 102(b) And 103(a) Should Be Reversed

1. The Rejection Of Claims 10, 16-18 And 23-32 Under 35 U.S.C. § 102(b) As Anticipated By European Patent Application No. 580 860 A1 To Nakamichi *et al.* (“Nakamichi”) Should Be Reversed

Claims 10, 16-18 and 23-32 have been rejected under 35 U.S.C. § 102(b) by the Final Office Action mailed on October 19, 2009. The rejection of claims 10, 16-18 and 23-32 should be reversed because Nakamichi does not disclose the claimed subject matter, and thus, cannot anticipate the claimed subject matter.

According to the Examiner, Nakamichi teaches a method of manufacturing a pharmaceutical solid dispersion, produced without heating chemicals and polymeric carriers above their respective melting points. However, the solid dispersions of Nakamichi are not controlled released dispersions and are not vitrified, which is each required by the pending claims. Appellants invite the Board’s attention to Figures 1, 3, 5, 6, 8, 10 and 12 which show that the solid dispersions of Nakamichi either release essentially no active ingredient or release essentially all of the active ingredient quickly. With regard to the Examiner’s citation

to test example 7, Appellants note that the formulation of test example 7 is found in the description of Example 5 on page 7, lines 49-55 of Nakamichi, which indicates that the compositions tested contained 5% (w/w) triacetin, a plasticizer used to lower the transition temperature of a polymer (see Nakamichi at page 3, lines 33-46). The controlled release matrices of the present invention do not contain a plasticizer, or any other type of compound used to lower the transition temperature of a polymer. Thus, not only do the controlled release matrices of the present claims differ from those of Nakamichi by being vitrified, they differ in that they do not contain a plasticizer to lower the transition temperature of a polymer. In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). None of the pending claims is explicitly anticipated by the disclosure of Nakamichi since none of the solid dispersions taught by Nakamichi are vitrified, controlled release dispersions. With regard to the Examiner's comments on the release profiles in the buffers at two different pH values being different from that in the body, Appellants point out the reason why two different pH values are used is because the solid dispersions being tested are enteric coated dispersions. As is understood by those of skill in the art, enteric coated dispersions are meant to protect the active agent from being released in the stomach, *i.e.*, at low pH.

Furthermore, with regard to the Examiner's comment that the examples in Nakamichi are solely for the purpose of illustration, Appellants note that the examples set forth in Nakamichi are essentially the entire disclosure. Further, case law requires that for a rejection of anticipation, the reference must disclose each and every element of the claim; however, Nakamichi does not disclose each and every element of the claims, *i.e.*, that the dispersions are controlled release and are vitrified.

In view of the foregoing, Appellant submits that this rejection should be reversed and that the claimed controlled release matrices set forth in claims 10, 16-18 and 23-32 are not anticipated.

2. **The Rejection Of Claims 10, 16, 17 And 23-32 Under 35 U.S.C. § 102(b) As Anticipated By International Patent Application Publication No. WO 92/15285 to Lentz et al. ("Lentz") Should Be Reversed**

Claims 10, 16, 17 and 23-32 have been rejected under 35 U.S.C. § 102(b) by the Final Office Action mailed on October 19, 2009. The rejection of claims 10, 16, 17 and 23-32 should be reversed because Lentz does not disclose the claimed subject matter, and thus, cannot anticipate the claimed subject matter.

Appellants note that none of the rejected claims, directed to controlled release matrices, is explicitly anticipated by the disclosure of Lentz since Lentz does not disclose such controlled release matrices. Appellants submit that the Examiner is improperly combining one teaching of Lentz with regard to processing starch and combining the processed starch with an active agent and the teaching in Lentz with regard to co-extruding previously processed starch with an active agent. The present claims are limited to compositions produced by co-extrusion which are different from the sole co-extruded composition of Lentz. The Examiner asserts that this example is not meant to be limiting, but Appellants assert that it fully exemplifies the disclosure of Lentz with regard to co-extruding a pharmaceutically active agent with the molecularly dispersed starch (MDS) taught in Lentz. Even though both Lentz and the present invention teach destructure of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lentz is soft and rubbery and, thus, above glass transition temperature. In fact, Lentz teaches at page 14, lines 6-25, that it is preferred that the process heats the starch above the glass transition temperature. Moreover, Appellants invite the Examiner's attention to page 12, lines 5-25 of Lentz, which discusses that the formation of molecularly dispersed starch (MDS) requires that the starch being melted above its glass transition temperature. It is this MDS that Lentz co-extrudes.

In contrast, the extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains below the glass transition temperature, as specified in the claims. Further, Appellants have provided experimental evidence comparing the process of the present invention, where the temperature of the extruder orifice is below 100°C, with the process taught by Lentz, where the temperature of the extruder orifice is 240°C. The Board's attention is invited to the Rein Declaration at Paragraphs 8 to 12, which was submitted originally with the Reply under 37 C.F.R. § 1.111 on February 12, 2007, and a copy of which

is submitted herewith. In the Declaration, Dr. Rein sets forth experiments that were performed or supervised and directed by him, and their results demonstrating that using the process of Lentz (over 100°C) only popped (foamed) products are produced, whereas using the process of the present invention (under 100°C) a vitrified product is produced, which product is a controlled-release product. Thus, this experimental evidence overwhelmingly shows that two different products are produced using the two different methods.

Moreover, Appellants note that Figure 6 of Lentz shows that when the water content is less than 15.8%, the tablets are no longer controlled release tablets. This is in contrast to the presently pending claims which require that the water content be 15% or less. Thus, Lentz does not disclose controlled release compositions with water content as specified in the claims of the instant application.

In view of the foregoing, Appellant submits that this rejection should be reversed and that the claimed controlled release matrices set forth in claims 10, 16, 17 and 23-32 are not anticipated.

3. The Rejection Of Claims 1, 5, 6, 10, 16-18 And 20-32 Under 35 U.S.C. § 103(a) As Obvious In View Of European Patent Application No. 580 860 A1 To Nakamichi *et al.* (“Nakamichi”) Should Be Reversed

Claims 1, 5, 6, 10, 16-18 and 20-32 have been rejected under 35 U.S.C. § 103(a) over European Patent Application Publication No. 580 860 A1 to Nakamichi *et al.* (“Nakamichi”). The rejection of claims 1, 5, 6, 10, 16-18 and 20-32 should be reversed because the Examiner fails to make a *prima facie* case for obviousness. Not surprisingly, Nakamichi also lacks a teaching, suggestion or motivation for one skilled in the art to modify various parameters to achieve the claimed methods and controlled release products.

The Examiner alleges that Nakamichi is silent on certain parameters of the extrusion process but that it would have been obvious for one skilled in the art to optimize such parameters to obtain the desired product.

Appellants respectfully disagree. In order to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Additionally, the Supreme Court, in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q. 1385 (2007), affirmed that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,” and that it is “important

to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR*, S.Ct. at 1741, 82 U.S.P.Q.2d at 1396. Further, under *KSR*, “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR*, S.Ct. at 1740, 82 U.S.P.Q.2d at 1396. The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O’Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

In the instant application, the claims are directed to methods of co-extrusion under specified conditions and to the controlled release matrices that result from the methods of co-extrusion. While Appellants would not dispute that, in certain instances, the optimization of a parameter may be obvious; however, only in cases where the cited prior art teaches not only which parameter to optimize, but also what is the desired product. Appellants submit that the claimed invention is not obvious in view of Nakamichi since Nakamichi does not provide the skilled artisan with the teaching or suggestion of the product to be obtained or the teaching or suggestion of which extrusion parameters to adjust and how to adjust said parameters to achieve the desired product. In the instant case, Nakamichi does not teach or suggest which of the many parameters should be adjusted, if any, *e.g.*, temperature, pressure, amount of water, *etc.*, to achieve the desired result, and Nakamichi does not teach or suggest that a controlled release matrix or a method of obtaining such a controlled release matrix are the desired product. Appellants submit that it would be undue experimentation to try to achieve the claimed invention based on the teachings of Nakamichi. Nakamichi does not provide the person of skill in the art the required reasonable expectation of success to achieve the co-extrusion methods and controlled release compositions claimed in the present application, thus, Nakamichi does not render the claimed invention obvious.

In view of the foregoing, Appellant submits that this rejection should be reversed and that the claimed methods and controlled release matrices set forth in claims 1, 5, 6, 10, 16-18 and 20-32 are not obvious in view of the disclosure of Nakamichi.

4. **The Rejection Of Claims 1, 5, 6, 10, 16-18 And 20-32 Under 35 U.S.C. § 103(a) As Obvious In View Of International Patent Application Publication No. WO 92/15285 to Lentz *et al.* ("Lentz") Should Be Reversed**

Claims 1, 5, 6, 10, 16-18 and 20-32 have been rejected under 35 U.S.C. § 103(a) over International Patent Application Publication No. WO 92/15258 to Lentz *et al.* ("Lentz"). The rejection of claims 1, 5, 6, 10, 16-18 and 20-32 should be reversed because the Examiner fails to make a *prima facie* case for obviousness. Not surprisingly, Lentz also lacks a teaching, suggestion or motivation for one skilled in the art to modify various parameters to achieve the claimed methods and controlled release products.

Lenz discloses compositions comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80°C to 240°C in a closed volume wherein the water content of the matrix was maintained at about 5% to about 45% by weight based on the starch/water mix, and (ii) an active ingredient. Preferably, the starch is processed to a specific endothermic transition just prior to oxidation and thermal degradation. Note that the active ingredient is not processed with the starch but is merely combined with the starch after processing. See Lenz at page 11, lines 13-25; at page 14, lines 16-25. Moreover, the processed starch in Lenz, called molecularly dispersed starch or MDS, is not stiff or glassy, but, rather, is soft and rubbery, which allows the extruded MDS to be more compressible. See Lenz at page 28, lines 31-38, which teaches that the MDS obtained by extrusion is soft and rubbery. Even though both Lentz and the present invention teach destructure of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lenz is soft and rubbery and, thus, above glass transition temperature. In fact, Lenz teaches at page 14, lines 6-25, that it is preferred that the process heats the starch above the glass transition temperature. The extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains below the glass transition temperature. This structural differences between the starch matrices of the present invention and that of Lentz is a consequence of the differences in the disclosed methods, *inter alia*, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure.

The only passage in Lenz that concerns co-extrusion of a pharmaceutically active agent and a starch is on page 17, line 37 to page 18, line 1. However, there are absolutely no details in the Lenz specification on how such a co-extrusion can be carried out, unless the co-

extrusion is carried out by the same methodology as Lenz uses to extrude the starch alone. Simply stating that co-extrusion is desirable cannot suggest the specific methods of the present invention. Appellants point out that Example 18 in Lenz, however, does provide details for a method of co-extrusion. However, Example 18 teaches co-extrusion of not starch but molecularly dispersed starch (which was previously extruded starch) with an active agent (clotrimazole) and talc. Further, as explicitly stated by Lenz, the resulting co-extruded product is a foamed product, which is not a controlled release matrix. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix. A foamed product is not a vitrified product.

The Examiner has criticized Appellants for interpreting Lenz based solely on the Examples. Appellants submit that they have not done so. However, where the specification is silent on how to specifically carry out the co-extrusion, Appellants have no choice but to look to the sole Example where such a method of co-extrusion is disclosed for details on how to carry out the method in order to determine whether the method is the same or different from the claimed method, and whether any differences are meaningful. Only once it is determined what the actual methodology entails, can one skilled in the art determine whether the disclosure of Lenz fills in the gap between the teaching of Lenz and the claimed invention. Appellants respectfully submit that the differences between the presently claimed methods and Lenz, *i.e.*, that the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure resulting in the production of a vitrified controlled release matrix, are not obvious in view of Lenz since Lenz does not suggest such specific methodology nor to modify the disclosed method to achieve the claimed methods. Further, with regard to the extruded product itself, Lenz does not teach or suggest such a vitrified product nor does Lenz teach or suggest how to modify the disclosed method to produce such a vitrified controlled release matrix.

Lenz teaches throughout the specification, including the Examples, the production of a starting material for a controlled release matrix. As taught on page 11, lines 26 to 29 of Lenz, the extrusion process only serves to destructure the starch to obtain the starting material, molecularly dispersed starch or MDS, which MDS is then processed further. Lenz clearly teaches that the MDS is only subsequently, *i.e.*, after the extrusion step, processed into a controlled release dosage form. Lenz does not suggest that the extruded starch, whether co-extruded with an active agent or not, can be used as a controlled release product prior to any other further processing. Page 15, lines 8-14 of Lenz discloses that controlled release is a consequence of the improved compressibility and/or density of the dosage form, thus,

indicating that controlled release functionality is obtained upon compressing the MDS and active agent, *e.g.*, into a tablet. Thus, Lentz clearly discloses that the extrusion of the starch only serves to produce MDS as the starting material for further processing into a controlled release preparation. The controlled release matrix of Lentz is not directly obtained through extrusion even if the starch was co-extruded with the active agent. Such controlled release functionality is disclosed to be only a consequence of additional processing steps.

Further, Appellants invite the Board's attention to the Declaration of Dr. Hubert Rein under 37 C.F.R. § 1.132 ("the Rein Declaration"), originally submitted with the Reply under 37 C.F.R. § 1.111 on February 12, 2007. In particular, Dr. Rein, a co-inventor of the present invention, in Paragraph 6 states:

Importantly, the teaching of Lentz regarding the temperature range of 80°C to 240°C for processing does not mean that the processing can take place at any temperature between 80°C to 240°C but rather means that the entire process occurs at temperatures encompassing 80°C to 240°C, never just at 80°C or 130°C or 240°C. This is an important distinction as, contrary to the Examiner's assertion, there are no overlapping temperatures between the two processes. One skilled in the art of extrusion would clearly understand that Lentz is giving the range of the temperatures of the extruder, which temperatures differ at different locations of the extruder. Lentz specifically teaches on page 28, lines 17-19 that the extruder barrel temperature profile was 80°C - 160°C - 240°C (for feed, screw and die, respectively). One skilled in the art would understand that the temperature of the extruder orifice (die) is 240°C. This is an important distinction between the teachings of Lentz and the presently claimed invention, where the orifice of the extruder is below 100°C, which also means that all other parts of the extruder are below 100°C.

Further, Dr. Rein states in Paragraph 7:

The only passage in Lentz that concerns co-extrusion of a pharmaceutically active agent and a starch is on page 17, line 37 to page 18, line 1. However, there are absolutely no details in the Lentz specification to teach one skilled in the art how such a co-extrusion can be carried out, unless the co-extrusion is carried out by the same methodology as Lentz uses to extrude the starch alone. Example 18 in Lentz, however, does provide details for a method of co-extrusion. However, Example 18 teaches co-extrusion of not starch but molecularly dispersed starch (which was previously extruded starch) with an active agent (clotrimazole) and talc. Further, as explicitly stated by Lentz, the resulting co-extruded product is a foamed, rubbery product, which is not a controlled release matrix. The pending claims require that the matrix produced by the method be a vitrified controlled release

matrix, *i.e.*, glassy. A foamed, rubbery product is not a glassy vitrified product.

Thus, not only does Lentz not teach or suggest any overlapping temperatures for the extrusion process, in the only co-extrusion example set forth in Lentz, the result was a foamy, rubbery product that is not a controlled-release product.

Moreover, experimental evidence comparing the process of the present invention was provided, where the temperature of the extruder orifice is below 100°C, with the process taught by Lentz, where the temperature of the extruder orifice is 240°C. The Examiner's attention is invited to the Rein Declaration at Paragraphs 8 to 12 where Dr. Rein sets forth experiments that were performed or supervised and directed by him, and their results demonstrating that using the process of Lentz (over 100°C) only popped (foamed) products are produced, whereas using the process of the present invention (under 100°C) a vitrified product is produced, which product is a controlled-release product. Thus, this experimental evidence overwhelmingly shows that two different products are produced using the two different methods.

Moreover, Appellants submit that the Declaration of Dr. Rein fully supports the full breadth of the claims. Appellants note that experiments disclosed in the present specification as originally filed provide a temperature profile of 65°C-80°C-98°C, thus encompassing a die temperature of under 100°C. Furthermore, Appellants note that Dr. Rein not only performed an experiment with a temperature profile 80°C-80°C-80°C, but also performed experiments with die temperatures of 97°C, 100°C, 102°C, and 114°C. Thus, the specification as originally filed already provides examples covering co-extrusion at a die temperature of less than 100°C and Dr. Rein subsequently showed by the submitted experimental data that, if one were to co-extrude at a die temperature of less than 100°C, one would obtain vitrified products with controlled release properties. Thus, evidence has been presented that covers the full breadth of the claims.

Furthermore, Appellants note that with regard to the Examiner's use of the specific examples in Figure 10, Appellants point out that the claimed methods specifically recite temperatures below 100°C. Thus, three of the four specific examples in Figure 10 of Lentz, 160°C, 130°C, and 100°C, fall outside the claims, not two as alleged by the Examiner. Further, the sole temperature below 100°C in Figure 10 is 70°C. However, this temperature does not produce a controlled release matrix, but rather a quick release dispersion. Thus, Lentz teaches that extrusion at the sole temperature that falls within the claims produces a quick release dispersion, not a controlled release dispersion. Based on this example,

Appellants submit that Lentz also teaches away from the claimed invention. Moreover, Appellants note that starch extruded in the experiment summarized in Figure 10 is MDS starch, which starch is not vitrified, as discussed below.

The Examiner is invited to page 12, lines 5-25 of Lentz, which teaches three different temperature levels for three different levels of destructuralization of starch, and that the third level involving the highest temperatures, where the glass transition temperature is exceeded, results in the production of molecularly dispersed starch (MDS), and which can result in a controlled release dispersion. As discussed above, the MDS taught in Lentz is not vitrified, and this passage on page 12 clearly indicates that the MDS of Lentz can not be vitrified since the glass transition temperature has been exceeded in producing the MDS. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix, *i.e.*, glassy. Appellants do not find it reasonable to interpret the disclosure of Lentz to include the teaching or suggestion of a controlled-release product produced by co-extrusion below 100°C. Lentz does not teach or suggest a modification of its disclosed method requiring that the temperature at the orifice of the extruder (as well as all other parts of the extruder) during the extrusion process be below 100°C under normal pressure. Indeed, the only disclosed specific experimental conditions for processing starch are found in Example 1 of Lentz and the molecularly dispersed starch (MDS) produced in Example 1 is used throughout all other experiments, including the co-extrusion experiment in Example 18. Appellants submit that the MDS produced according to Example 1 is, indeed, representative of the MDS used in all other experiments disclosed in Lentz, which MDS is not the same as nor suggestive of the co-extruded compositions of the present invention, since the glass transition of the starch was exceeded in producing the MDS, which means that MDS is not vitrified starch. Appellants maintain the position that it is unreasonable for the Examiner to extrapolate the disclosure of Lentz to suggest the co-extrusion of starch and an active agent at a die temperature of less than 100°C.

A rejection for obviousness is improper when there is nothing in the cited prior art reference suggests the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the

disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). In the present case, the presently claimed methods are directed to the production of a controlled release matrix by co-extrusion of a dry mixture of a starch and an active agent where the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure. Lentz does not teach or suggest a modification of its disclosed method requiring that the temperature at the orifice of the extruder (as well as all other parts of the extruder) during the extrusion process be below 100°C under normal pressure. Lentz does not teach or suggest that the temperature be kept under 100°C, and the only time Lentz actually co-extruded an active agent with its molecularly dispersed starch, no controlled release product was achieved. Lentz does not and cannot render the claimed invention obvious.

In view of the foregoing, Appellants submit that this rejection should be reversed and that the claimed methods and controlled release matrices set forth in claims 1, 5, 6, 10, 16-18 and 20-32 are not obvious in view of the disclosure of Lentz.

5. Summary

Appellants submit that neither of the cited references anticipates or renders obvious the claimed methods of producing a controlled release matrix, or a matrix produced by such methods.

VIII. CLAIMS APPENDIX

As noted in Section III above, an appendix containing a copy of the claims involved in this appeal is submitted herewith.

IX. EVIDENCE APPENDIX

Appellants submitted a Declaration of Dr. Hubert Rein under 37 C.F.R. § 1.132 during the prosecution of the present application, an additional copy of which is submitted herewith.

X. RELATED PROCEEDINGS APPENDIX

As noted in Section II above, Appellants are not aware of any proceeding or interference which may be related to, directly affect or be directly affected by or having a bearing on the Board's decision in the pending appeal.


XI. CONCLUSION

Appellants respectfully submit that the rejections of claims 1, 5, 6, 10, 16-18 and 20-32 under 35 U.S.C. §§ 102(b) and 103(a) as being anticipated by or obvious over Nakamichi or Lentz are improper and should be withdrawn. Further, claims 1, 5, 6, 10, 16-18 and 20-32 are allowable in view of the record.

Therefore, for all of the reasons set forth above, Appellants respectfully request that all of the claims on appeal be declared allowable.

Respectfully submitted,

Date: October 29, 2010


William J. Thomann 40,203
(Reg. No.)
Jones Day
222 East 41st Street
New York, New York 10017

CLAIMS APPENDIX

CLAIMS ON APPEAL

U.S. APPLICATION NO. 09/980,727
ATTORNEY DOCKET NO. 11390-009-999

1. A method for producing a controlled release matrix, comprising co-extruding through an extruder a composition comprising a dry mixture of at least one pharmaceutically active agent and at least one starch, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure, and wherein the co-extruding is under sheer force, temperature and pressure conditions such that the starch in the extruded controlled release matrix is vitrified.

Claims 2-3 are canceled.

4. The method of claim 1, wherein up to 15% by weight water is added to the composition prior to co-extruding.

5. The method of claim 1, wherein the matrix is water-insoluble.

6. The method of claim 1, wherein the co-extruding is under shear force, temperature, and pressure conditions to achieve glass transition of the starch.

Claims 7-9 are canceled.

10. A controlled release matrix produced by the method of claim 1, 4, 5, 20, 21 or 22.

Claims 11-15 are canceled.

16. The matrix of claim 10, wherein the release of the pharmaceutically active agent from the matrix substantially follows the lapidus rule.

17. The matrix of claim 10, wherein the release of the pharmaceutically active agent from the matrix is over 24 hours or more.

18. The matrix of claim 10, wherein the pharmaceutically active agent is present in the matrix as a liquid.

Claim 19 is canceled.

20. The method of claim 1, further comprising processing the matrix into granulates or into a mono-block pharmaceutical dosage form.

21. The method of claim 1, wherein the temperature in the feed area of the extruder is about 65°C, the temperature in the screw area is about 80°C, and the temperature in the die is about 98°C.

22. The method of claim 1, wherein the starch is selected from the group consisting of tapioca starch, wheat starch, potato starch, corn starch, acetylic starch, partially pregelatinized starch, wax corn starch, amylo corn starch, and a mixture of any of the foregoing.

23. The matrix of claim 10, wherein the pharmaceutically active agent is present in the matrix as a solid.

24. The matrix of claim 10, wherein the pharmaceutically active agent is dissolved in the matrix.

25. A controlled release matrix, comprising at least one starch and at least one pharmaceutically active agent, wherein the starch in the matrix is vitrified, and wherein the starch and pharmaceutically active agent were co-extruded.

26. The matrix of claim 25, wherein the matrix is free of pores.

27. The matrix of claim 25, which is water-insoluble.

28. The matrix of claim 25, wherein the pharmaceutically active agent is present in the matrix as a liquid.

29. The matrix of claim 25, wherein the pharmaceutically active agent is present in the matrix as a solid.

30. The matrix of claim 25, wherein the pharmaceutically active agent is dissolved in the matrix.

31. The matrix of claim 25, wherein the release of the pharmaceutically active agent from the matrix substantially follows the lapidus rule.

32. The matrix of claim 25, wherein the release of the pharmaceutically active agent from the matrix is over 24 hours or more.

Electronically Filed

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Rein *et al.*

Confirmation No.: 8812

Serial No.: 09/980,727

Group Art Unit: 1618

Filed: July 8, 2002

Examiner: Rogers, James William

For: METHOD FOR PRODUCING A WATER-
INSOLUBLE AMORPHOUS OR PARTIALLY
AMORPHOUS CONTROLLED-RELEASE
MATRIX

Attorney Docket No.: 11390-009

Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Rein *et al.*

Confirmation No.: 8812

Serial No.: 09/980,727

Art Unit: 1615

Filed: July 8, 2002

Examiner: Simon J. Oh

For: METHOD FOR PRODUCING A WATER-
INSOLUBLE AMORPHOUS OR PARTIALLY
AMORPHOUS CONTROLLED-RELEASE
MATRIX

Attorney Docket No.: 11390-009

DECLARATION OF DR. HUBERT REIN UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Hubert Rein, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application.
2. I am currently Privatdozent at the University of Bonn.
3. My academic background and technical experience are set forth in my *curriculum vitae*, attached hereto as Exhibit 1.
4. I have reviewed the above-identified patent application, the pending claims, and the Office Action mailed January 11, 2006. I understand that the Examiner has rejected the claims under 35 U.S.C. § 103(a), on the allegation that International Publication No. WO 92/15285 to Lentz *et al.* ("Lentz") renders obvious the claimed methods and matrices produced thereby due to an alleged overlap in the temperature parameters.
5. I have reviewed the Lentz *et al.* patent publication. Lentz discloses compositions comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80 °C to 240 °C in a closed volume wherein the water content of the

NYT-3962990v1

matrix was maintained at about 5% to about 45% by weight based on the starch/water mix, and (ii) an active ingredient. Preferably, the starch is processed to a specific endothermic transition just prior to oxidation and thermal degradation. Note that the active ingredient is not processed with the starch but is merely combined with the starch after processing. See Lentz at page 11, lines 13-25; at page 14, lines 16-25. Moreover, the processed starch in Lentz, called molecularly dispersed starch or MDS, is not stiff or glassy, but, rather, is soft and rubbery, which allows the extruded MDS to be more compressible. See Lentz at page 28, lines 31-38, which teaches that the MDS obtained by extrusion is soft and rubbery. Even though both Lentz and the present invention teach destructure of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lentz is soft and rubbery and, thus, above glass transition temperature. In fact, Lentz teaches at page 14, lines 6-25, that it is preferred that the process heats the starch above the glass transition temperature. In contrast, the extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains below the glass transition temperature. This structural difference between the starch matrices of the present invention and that of Lentz is a consequence of the differences in the disclosed methods, *inter alia*, wherein the temperature at the orifice of the extruder during the extrusion process is below 100 °C under normal pressure.

6. Importantly, the teaching of Lentz regarding the temperature range of 80 °C to 240 °C for processing does not mean that the processing can take place at any temperature between 80 °C to 240 °C but rather means that the entire process occurs at temperature encompassing 80 °C to 240 °C, never just at 80 °C or 130 °C or 240 °C. This is an important distinction as, contrary to the Examiner's assertion, there are no overlapping temperatures between the two processes. One skilled in the art of extrusion would clearly understand that Lentz is giving the range of the temperatures of the extruder, which temperatures differ at different locations of the extruder. Lentz specifically teaches on page 28, lines 17-19 that the extruder barrel temperature profile was 80 °C – 160 °C – 240 °C (for feed, screw and die, respectively). One skilled in the art would understand that the temperature of the extruder orifice (die) is 240 °C. This is an important distinction between the teachings of Lentz and the presently claimed invention, where the orifice of the extruder is below 100 °C, which also means that all other parts of the extruder are below 100 °C.

7. The only passage in Lentz that concerns co-extrusion of a pharmaceutically active agent and a starch is on page 17, line 37 to page 18, line 1. However, there are absolutely no details in the Lentz specification to teach one skilled in the art how such a co-extrusion can be carried out, unless the co-extrusion is carried out by the same methodology as Lentz uses to extrude the starch alone. Example 18 in Lentz, however, does provide details for a method of co-extrusion. However, Example 18 teaches co-extrusion of not starch but molecularly dispersed starch (which was previously extruded starch) with an active agent (clotrimazole) and talc. Further, as explicitly stated by Lentz, the resulting co-extruded product is a foamed, rubbery product, which is not a controlled release matrix. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix, i.e., glassy. A foamed, rubbery product is not a glassy vitrified product.

8. Further, I have performed experiments and/or experiments have been performed under my supervision and direction demonstrating that using the process of Lentz (over 100 °C) only popped (foamed) products are produced, whereas using the process of the present invention (under 100 °C) a vitrified product is produced.

9. Attached as Exhibit 2 is a 30 page power point presentation entitled "Starch extrusion." This power point presentation details the experiments that were performed, namely comparing extrusion of a starch under the conditions taught in the present invention (DE 199 18 325 A1) and under the conditions taught in Lentz (WO 92/15285) using a Leistritz ZSE 27 HP 32 D extruder. On pages 4-6, results of extrusion of potato starch under the conditions of the present invention (at 80 °C) shows that the extrusion yielded a continuous strand of amorphous starch. However, raising the temperature to 114 °C resulted in popping-up of the exudates. Page 8 sets forth a summary of the products obtained at different die (extruder orifice) temperatures. Clearly, temperatures above 100 °C result in a popped product, not a vitrified product as required by the claims. In contrast, on page 12 the results of an extrusion process under the temperature conditions taught by Lentz using potato starch are shown. Basically nothing could be extruded as the extruder becomes completely blocked and the cylinder must be heated to above 300 °C in order to remove the starch (basically the starch had to be burned off). Pages 13 to 18 provide additional data demonstrating that temperatures above 100 °C lead to a popped-up product.

10. Page 20 of Exhibit 2 shows the design of four additional extrusion experiments and pages 21 to 28 show the results. Consistent with the above-data, when the

extrusion process takes place with temperatures under 100 °C a product of the claimed invention is produced. However, using temperature conditions taught in Lentz results in popped products that are not directly useable as a controlled-release dosage form. Page 29 concludes that the two different processes result in two different products.

11. Attached as Exhibit 3 is a power point slide setting forth additional evidence that extruding at high temperatures as taught by Lentz results in popped products. Further, Exhibit 4 is an Experimental Report summarizing the same experiments set forth on pages 20 to 28 of Exhibit 2.

12. In view of the foregoing, not only is the present invention nonobvious over Lentz due, for example, to the fact that there is no temperature overlap, but also the experimental evidence overwhelming shows that different products are produced using the two different methods.

13. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: 8.2.07


Hubert Rein

EXHIBIT 1

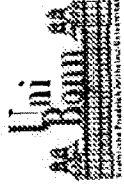
Dr. Hubert Rein
Eichenröder Weg 30
35396 Gießen-Wieseck

»Curriculum vitae«

Date of birth:	2. September 1961 in Gießen/Lahn	
Marital status:	Married, one child	
Nationality:	German	
School attendance:	September 1968 - June 1981	Käthe-Kollwitz-Grundschule, Gießen Friedrich-Ebert-Gymnasium, Wieseck Liebig-Oberschule, Gießen
	June 1981	Abitur, Examination subjects: Physics, chemistry, german, History
National service:	July 1981 - September 1982	
University education:	April 1984 - October 1987	Study of pharmacy, Philipps-Universität Marburg an der Lahn, Degree: Pharmazeut
Training: (Pharmaziepraktikant):	October 1987 - April 1988	Dünsberg-Apotheke, 35444 Rodheim
	May 1988 - September 1989	ASTA Werke AG, 33647 Brackwede Pharm. quality control
Promotion:	September 1993	
Habilitation:	December 2003	
Appointments:	December 1989	Approbation as Apotheker
	February 1990 - December 1993	Member of the Direktorium of the Institute of Pharm. Technology, Philipps-Universität-Marburg
	October 1994	Akademischer Rat of the Pharmazeutische Tech- nology, Universität Bonn
	October 1996	Official on lifetime
	October 1997	Member of the board of examiners of Pharmacy (Diplom), Universität Bonn
	January 2004	Privatdozent
Employments:	October 1982 - April 1984	Civil servant, Bundesanstalt für Arbeit (Federal employment office), Arbeitamt Gießen/Lahn

October 1988 - December 1989	Scientific assistant, Institut of Pharm. Technology, Philipps-Universität Marburg an der Lahn
January 1990 - December 1993	Scientific employee, Institut of Pharm. Technology, Universität Marbur an der Lahn
January 1994 - June 1994	Apotheker, Deutschhaus-Apotheke, Neukirchen/Schwalm
July 1994 - Sep- tember 1994	Apotheker, Thomae GmbH Biberach an der Riß, R&D, department solid forms
Since October 1994	Rat (lecturer) of the Pharm. Technology, Bonn
October 1995 - December 1996	C3-Professor of Pharm. Technology, Technische Universität Braunscheig

EXHIBIT 2

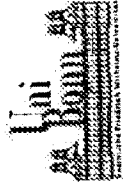


Starch extrusion

PD Dr. Hubert Rein

Pharmaceutical technology
Bonn-Endenich

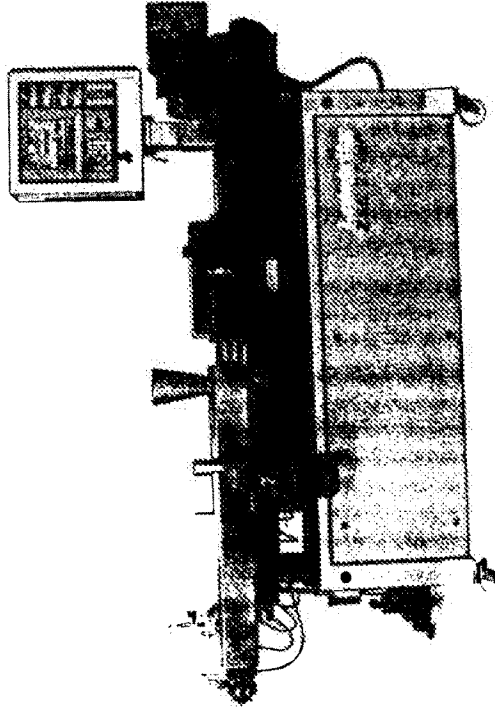




Starch extrusion: Overview

- **Extrusion according to DE 199 18 325A1**
production of a mono block form (Extrudette)
production of foamed extrudates (Xerogels)
- **Extrusion according to WO 92/15285 and US 4,673,438**

Extruder:



Leistritz ZSE 27 HP 32 D, Leistritz GmbH, Nürnberg

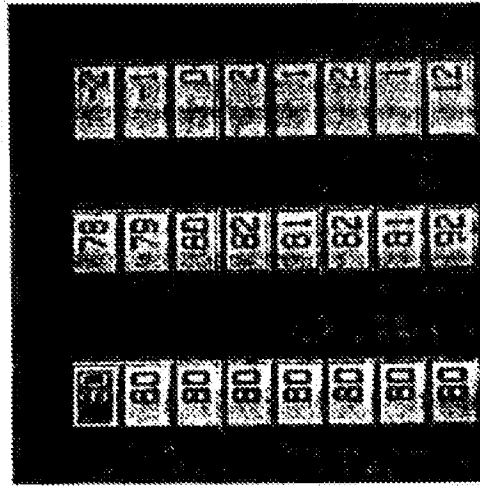
twin screw, co-rotating



Extrusion according to DE 199 18 325A

round orifice: 5 mm
temperature: 80 °C, Düse: 80 °C

E profil:



Temperature Display: ZSE 27



(for viewing click black panel)

Extrusion according to DE 199 18 325A1 yields a continuous strand of amorphous starch.



Extrusion according to DE 199 18 325A1

Pelletisation of the extruded strand of amorphous strand is possible without encountering problems.

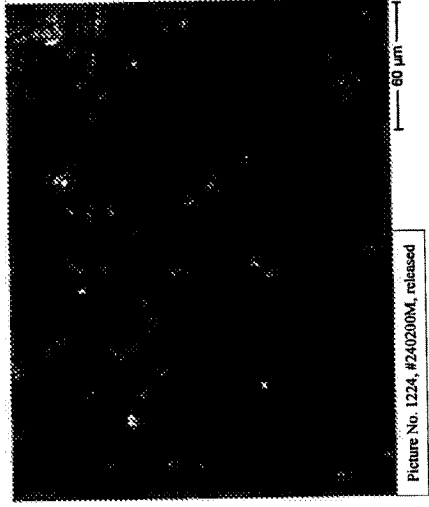
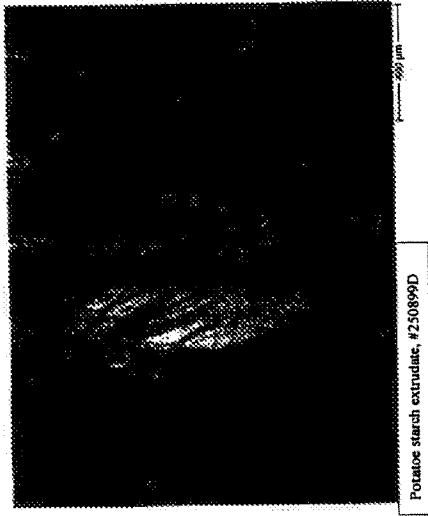


Example:
Hot cut with
rotating knife

Pilot plant station of
Leistriz GmbH Nürnberg

(for starting click black panel)

Extrusion according to DE 199 18 325A1



Scanning electron microscopy pictures

left: fracture surface of an extrudate of amorphous starch

right: fracture through the extrudate after release of the dispersed active agent. The negative imprints of formerly incorporated active agent crystals (caffeine) are clearly visible).



Extrusion according to DE 199 18 325A1

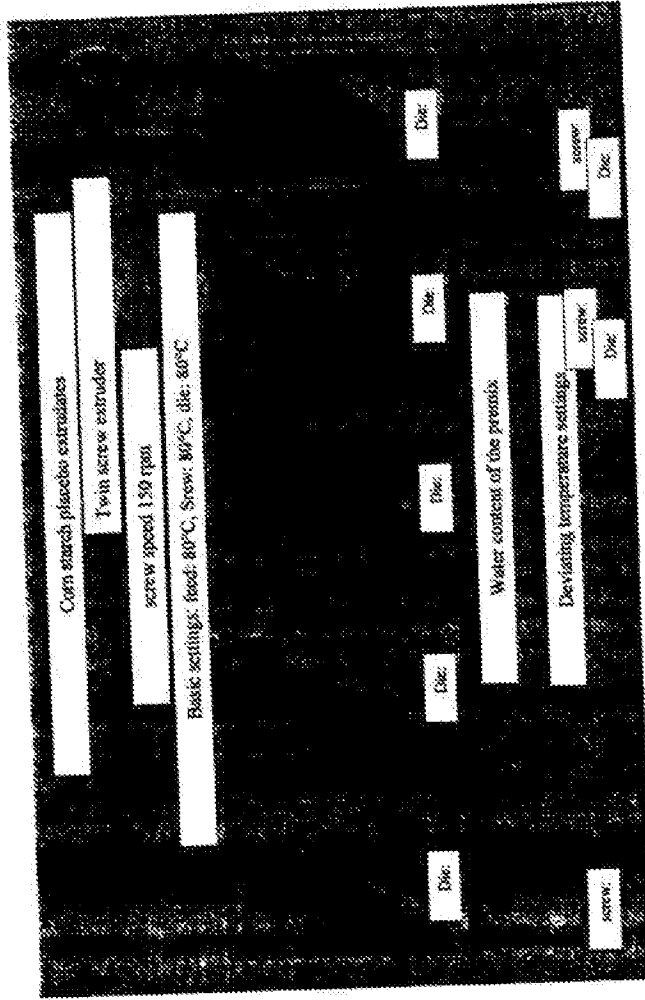
A temperature increase of the die segment from 80°C to 114°C leads to popping up of the extrudate



(click on black panel for starting)

Pilot plant station of
Leistritz GmbH Nürnberg

Extrusion according to DE 199 18 325A1



Product formation in dependence on temperature

Until 100 °C die temperature, one obtains a compact, cuttable extrudate. Higher temperatures lead to sudden evaporation of the incorporated water and popping up of the extrudate strand when leaving the die. (Ch.B.: 260203G).

Extrusion according to DE 199 18 325A1



- Extrusion according to **DE 199 18 325A1** allows production of mono block dosage forms of amorphous starch.
- The active agent can be dispersed or dissolved within the amorphous starch.
- Extrusion according to **DE 199 18 325A1** allows for so called one-excipient concept.
- Extrusion proceeds such that water which is incorporated in the product does not evaporate upon leaving the die. The product is therefore
 - a) free of bubbles and b) highly compact.



Stärkeextrusion nach US 4,673,438 und WO 92/15285

US 4,673,438 describes extrusion of potatoe starch (81 % potatoe starch, 19 % water, example 12) at a screw temperature of 110 to 130 °C and a die temperature of 130 °C.

As described, one can not obtain a non-popped product at a product temperature of about 130 °C and a water content of about 19%.

In WO 92/15285 more drastic conditions are used for extrusion: feed: 80 °C, screw 160 °C (Bsp. 11: 240 °C), die: 120 °C

At a temperature of 80 °C in the feeding section, the starch agglutinates before entering the extruder cylinder. Additionally, the extruder must be sealed towards ist rear end because if the high water vapor pressure in order to realise a screw temperature of 160°C in an aqueous surrounding.

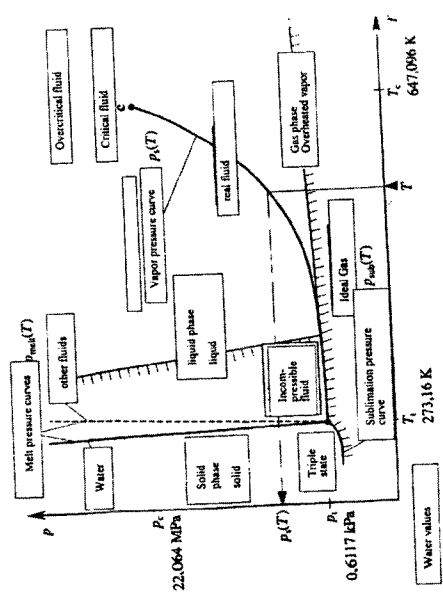
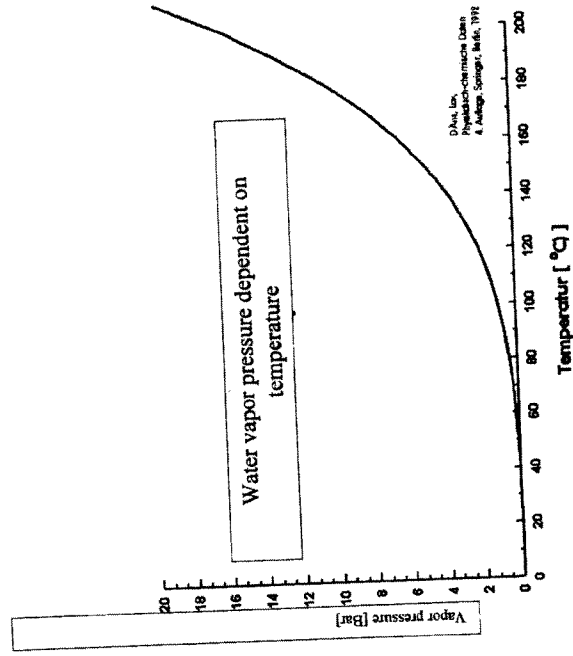
A controlled starch extrusion is not possible under these conditions.

See also following slide:

Phase diagram of water, vapor pressure development



Vapor pressure development of water in dependence of temperature



Source: Hering, Modler, Grundwissen des Ingenieurs, Fachbuchverlag Leipzig, 2002

Starch extrusion according to US 4,673,438 and WO 92/15285

- Any attempt to extrude potatoe starch under the conditions of the above patents leads within very short time to blocking of the extruder.
- The cylinder must be freed from starch by heating to above 300°C.



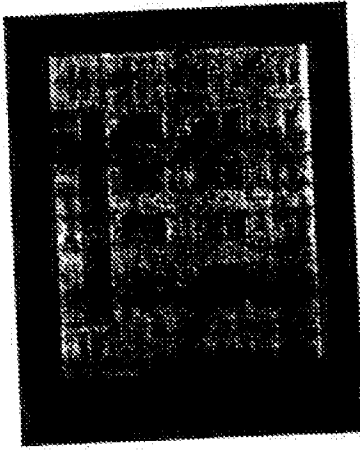
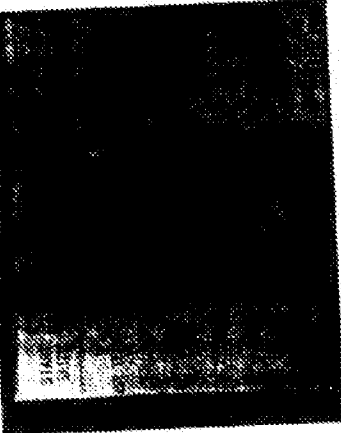
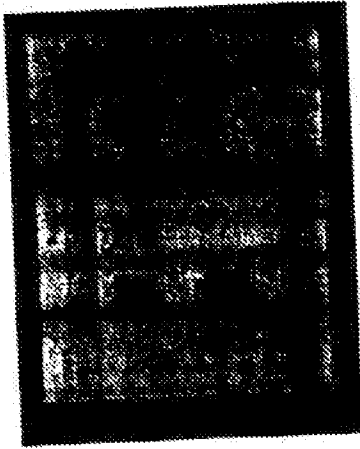
(click on black panel for start)

Pilot study plant of
Leistritz GmbH Nürnberg





Extrusion of potatoe starch with 19 % added water (without die)



Extrusion conditions DE 199 18 325A1

Screw temperature: 80 °C

The extruded mass is plastic and free of bubbles. Extrusion proceeds without problems.

Screw temperature:

80 to 90 °C

Slow increase in screw temperature to 90 °C; the product remains extrudable.

Screw temperature:

90 to 120 °C

The extrudate becomes vitrified (amorphous) and starts popping up at approximately 100°C. At 120°C the extrudate strand breaks, the extruder blocks.

Addition of further excipients to starch

Starch extrusion according to US 4,673,438 and WO 92/15285

In order to extrude starch at higher temperatures lubricants and plasticizers must be added to the starting mixture.

Recipe 1:

Placebo

Potatoe starch	810 g
Hydrated Triglyceride*	10 g
Sojalecithine	5 g
TiO ₂	5 g

Recipe 2:

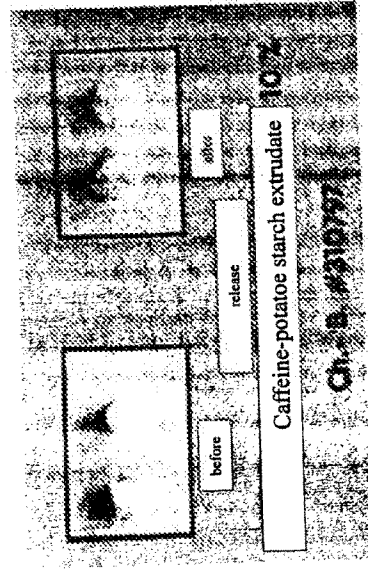
Potatoe starch	810 g
Hydrated Triglyceride*	10 g
Sojalecithine	5 g
TiO ₂	5 g
Tramadol * HCl	100 g

* e.g. hydrated peanut oil





Optical appearance of products according to DE 199 18 325A1, US 4,673,438 and WO 92/15285

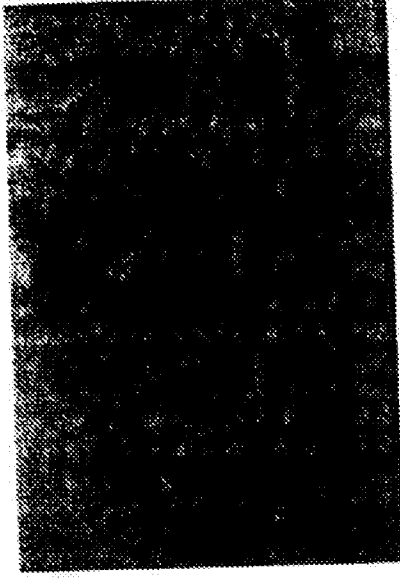


DE 199 18 325A1

Screw temperature: 66 °C, die temperature: 98 °C

The extrudate is compact and highly dense, no air bubbles are present.

The extrudate can be transformed into a ready to use dosage form (extrudette) by cutting into desired lengths. No further processing steps are necessary.



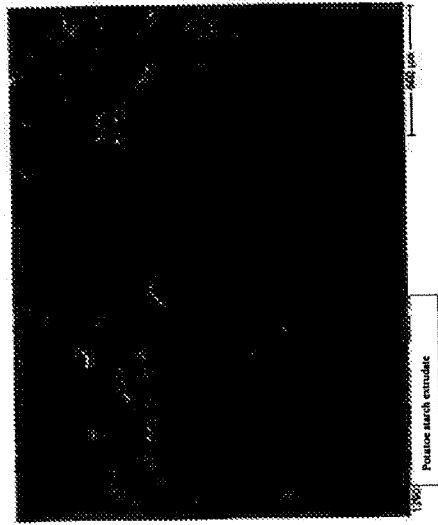
US 4,673,438 and WO 92/15285

One obtains a non-formable, coarse product with long curing time (several days).

Without further processing the extrudate is not suitable for use as a matrix in sustained release dosage forms.

Fig.: Extrudette bevor and after release according to Pharm. Eu. 4

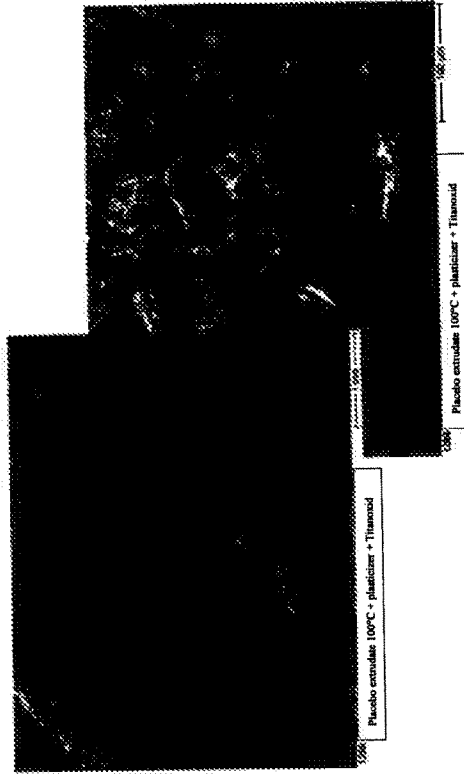
SEM-pictures of different starch extrudates



Potato starch extrudate

Extrusion without die, screw temperature 120 °C

Since the strand pops up, the extrudate is highly disrupted. The product is not suitable as a matrix without further processing.



Potato starch extrudate with plasticizer and pigment addition (Recipe 1):

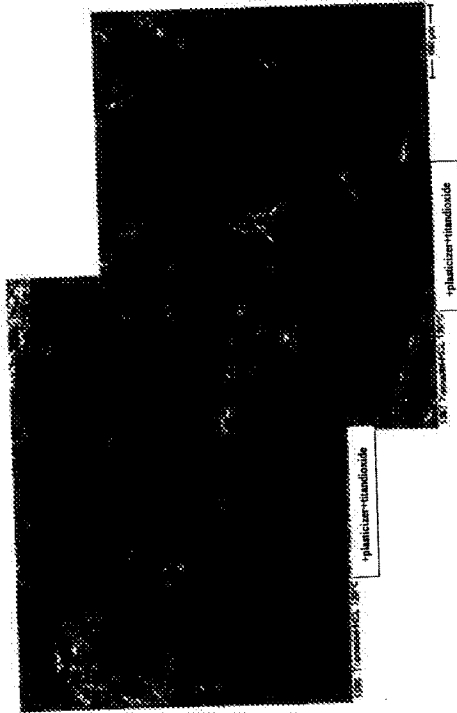
Extrusion without die, screw temperature 100 °C

In the extrudate one observes first voids which form by vapor evaporation. The starch is partly destructurized, but not completely amorphous.



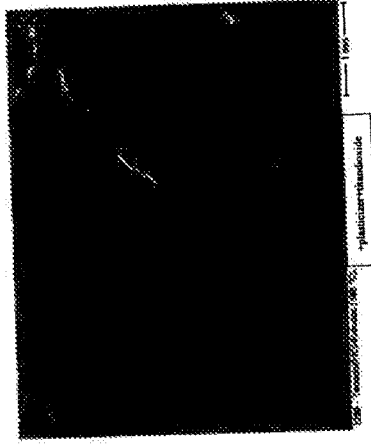
Extrudate with active agent potato starch + plasticizer + pigment (Recipe 2)

REM-Abbildungen



Screw temperature 120 °C

At a screw temperature of 120°C the extrudate is already heavily disrupted by the evaporating water. The energy input is insufficient to vitrify the starch completely. The single starch grains are clearly visible. The product is not suited for use as a matrix in a sustained release dosage form.



Screw temperature ca. 150 °C

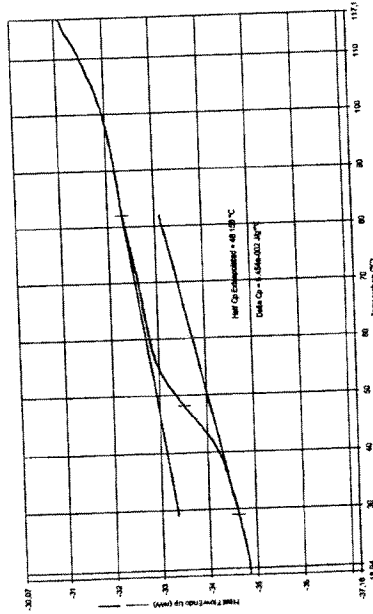
At a screw temperature of approximately 150°C an amorphous form of starch develops. The product is strongly swelled (Xerogel structure). Because of the lower density, the product is not suited for use as a matrix in a sustained release dosage form.



Glas transition temperatures T_g

The glas transition temperature T_g is a measure for thermal and mechanical stress of the extruded product. The higher T_g , the less sever is the production process.

The glas transition temperature should be at least 15°C above or below the application temperature of the dosage form (37 °C), in order to ensure a constant release behaviour.



Recipe 1, screw temperature 100 °C
 $T_g = 48$ °C

sample	Extrusion conditions	T_g [°C]
Potatoe starch DE 199 18 325A1	screw: 82 °C die: 98 °C	106
Potatoe starch	screw: 120 °C Without die	85
Recipe 1 Placebo extrudate	screw: 100 °C Without die	48
Recipe 2 Tramadol•HCl	screw: 120 °C Without die	51
Recipe 2 Tramadol•HCl	screw: 150 °C Without die	46

Method: PE HyperDLDK



Starch extrusion

Experiments of 22. December 2005

Addition of further excipients to the starch

starch extrusion of US 4,673,438 and WO 92/15285



The mixture described in US 4,673,438 and WO 92/15285 (Recipe

1) was extruded under various conditions:

Recipe 1:
Placebo

- Potatoe starch 810 g
- Hydrated Triglycerides 10 g
- Sojalecithine 5 g
- TiO₂ 5 g
- Water: 17%

Round die: 5 mm

221205	Temperature profil:
Exp. 1*	80 °C – 80 °C – 80 °C
Exp. 2	80 °C – 120 °C – 120 °C
Exp. 3	80 °C – 140 °C – 120 °C
Exp. 4**	80 °C – 160 °C – 120 °C

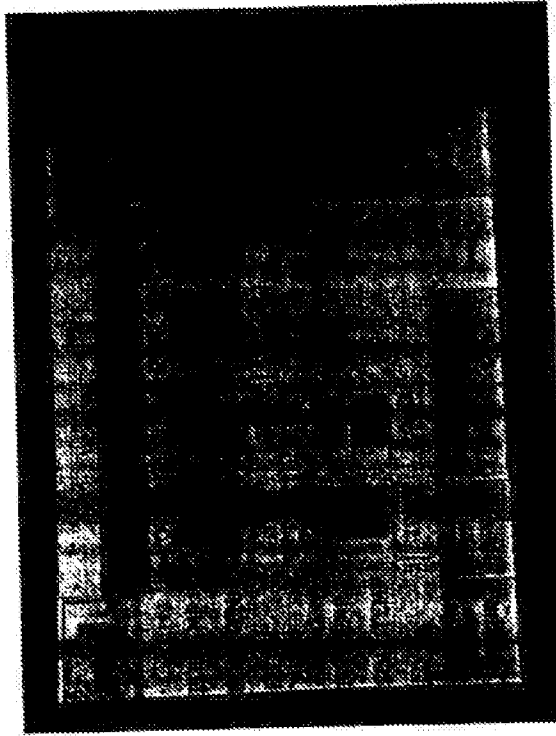
Screw speed: 75 U/Min.
Residence time (Exp 4): 75 s

* Extrusion conditions according to **DE 199 18 325A1**

** Extrusion conditions according to **US 4,673,438**

Starch extrusion: Exp. 1 (221205)

Temperature profil: 80 °C – 80 °C – 80 °C



- Extrusion proceeds without problems
- The product is partially popped.

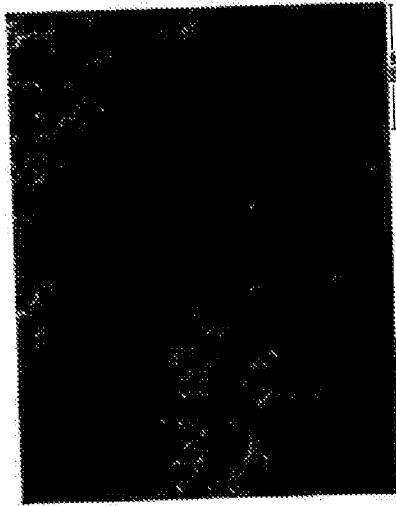
Extrusions according to
DE 199 18 325A1



Starch extrusion: Exp. 1 (221205)

Temperature profile: 80 °C – 80 °C – 80 °C

Product properties:



Potato starch mixture, 80 °C

Fracture surface



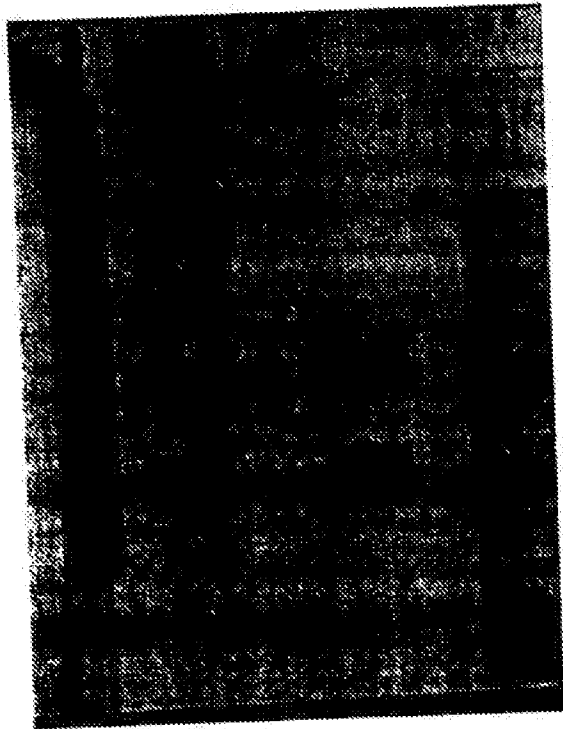
Product strand with multiple, non-vitrified starch grains;

Glas transition temperature: 85 °C

(Hyper-DSC^{WZ})

Starch extrusion: Exp. 2 (221205)

Temperature profile: 80 °C – 120 °C – 120 °C



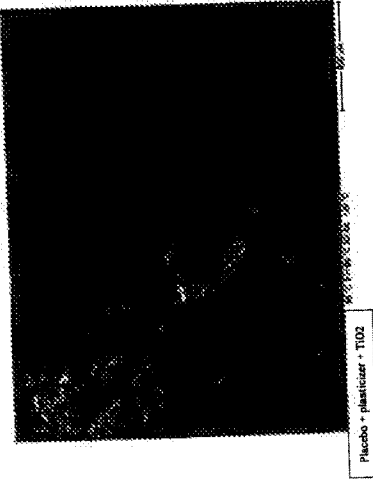
- Popped Product;
- Clear strand breakage;
- Extrudate is not suitable as a dosage form.



Starch extrusion: Exp. 2 (221205)

Temperature profile: 80 °C – 120 °C – 120 °C

Product properties:



Fracture surface



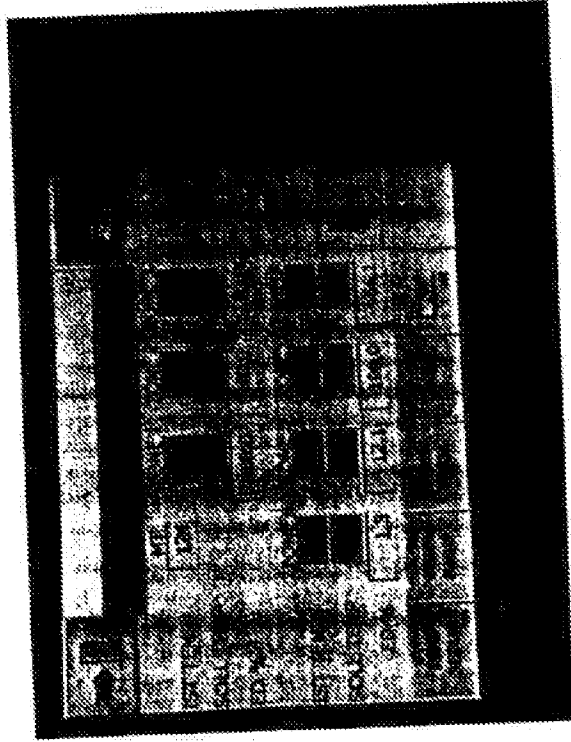
Heavily disrupted extrudate, not suitable as dosage form.

Glas transition temperature: 77 °C

(Hyper-DSC^{WZ})

Starch extrusion: Exp.3 (221205)

Temperature profile: 80 °C – 140 °C – 120 °C



- Non-controllable extrusion process;
- Foamed product;
- The incorporated water exits the die abruptly due to the high vapor pressure

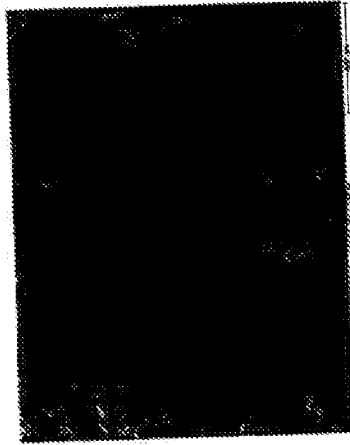




Starch extrusion: Exp. 3 (221205)

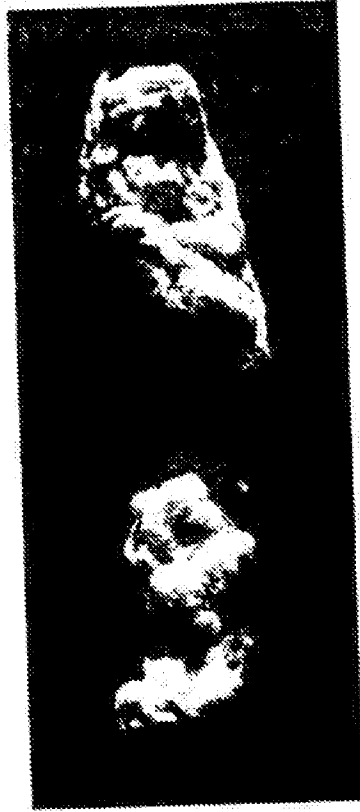
Temperature profile: 80 °C – 140 °C – 120 °C

Product properties:



Plastic + plasticizer + TO2

Fracture surface



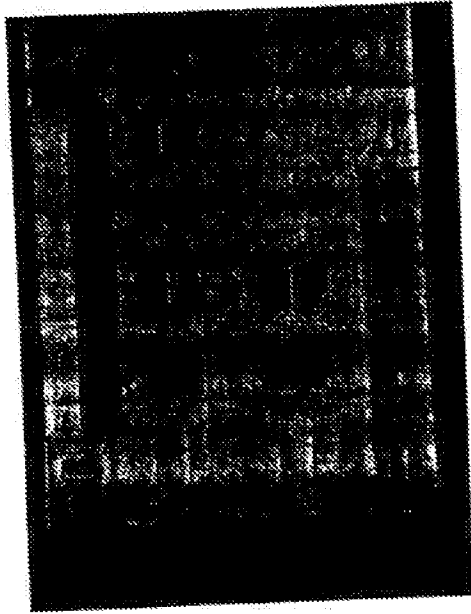
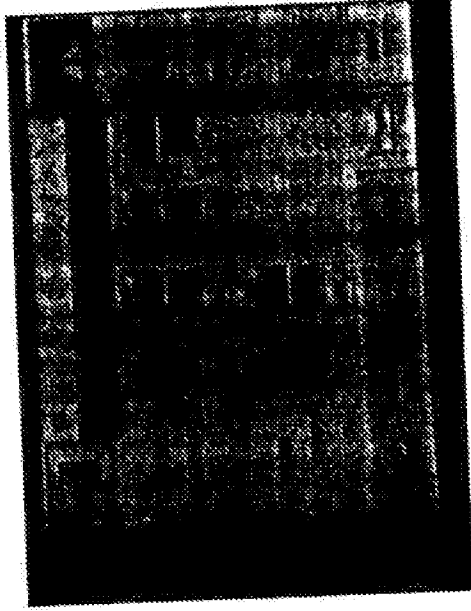
Foamed product, not suitable as mono block dosage form

Glas transition temperature: 75 °C

(Hyper-DSC^{WZ})

Starch extrusion: Exp. 4 (221205)

Temperature profile: 80 °C – 160 °C – 120 °C



When starting the extruder, water vapor exits the die with high pressure.

The extrusion process is not controllable. The foam that abruptly exits the die contains charred components due to the high temperature

Extrusion conditions according to US 4,673,438

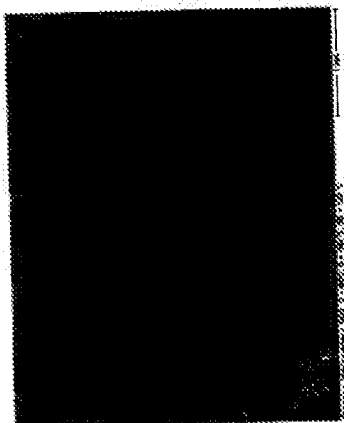
Starch extrusion: Exp. 4 (221205)

Temperature profile: 80 °C – 160 °C – 120 °C

Product properties:



Fracture surface



Fracture surface



Dry foam: The bubble walls are highly porous, the product is not suitable as a mono block dosage form.

Glas transition temperature: 67 °C

(Hyper-DSC^{WZ})

Extrusions conditions according to US 4,673,438

Conclusions

Extrusion processes as described in *DE 199 18 325A1* and *09/980 727* or *PCT/EP00/03612* lead to different products.

DE 199 18 325A1

- production of mono block sustained release dosage forms and granules is possible.
- Comparatively low thermal stress for the starting products.
- »One excipient concept« is possible.
- Führt auf direktem Weg zur fertigen Arzneiform.

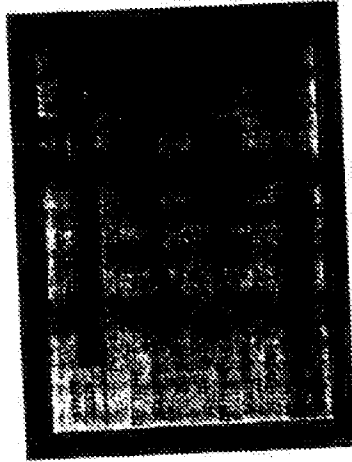
US 4,673,438 and WO 92/15285

- high thermal stress for starting substance
- TG in application window leads to release behaviour that is hard to calculate
- Extrusion – if at all – is possible only with additional excipients such as lubricants and plasticizers
- Extensive processing steps are necessary to obtain administratable dosage form
- Production of non-popped products is not possible.
- High bulk volume means voluminous dosage forms

EXHIBIT 3

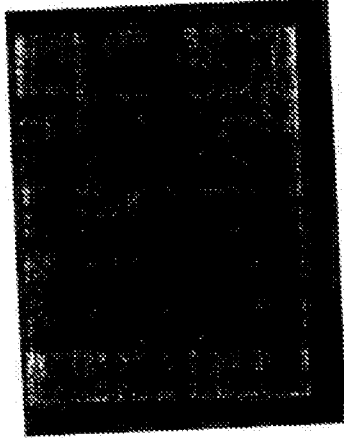
Addition of further excipients to the starch

Starch extrusion according to US 4,673,438 and WO 92/15285



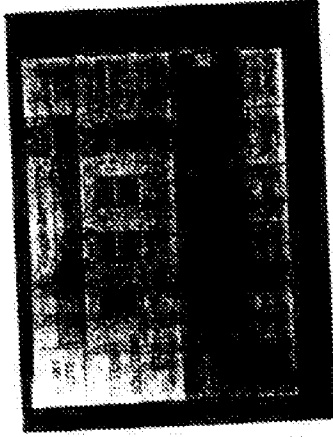
Extrusion at 80 – 100 °C
(Recipe 1)

The mixture can be extruded without problems.



Extrusion at 100 – 130 °C
(Recipe 2
with 10 % Tramadol*HCl

The mixture can be well extruded. As a product one obtains the flakes that are typical for this temperature. Partially, popping up occurs.



Extrusion at 160 °C
(Recipe 2
With 10 % Tramadol*HCl

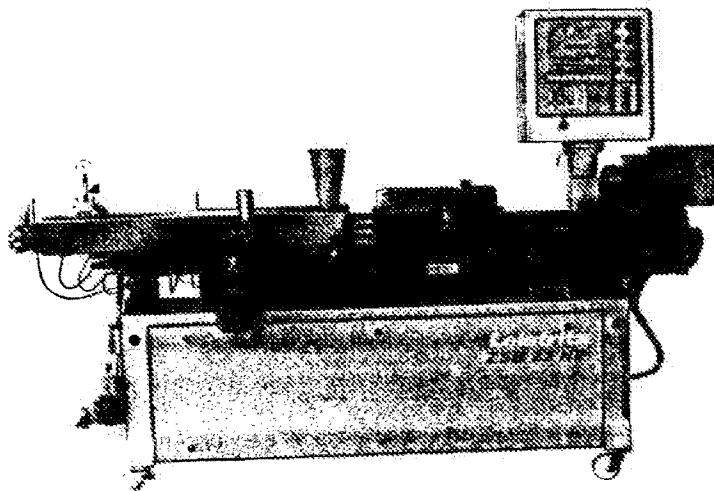
The mixture can be extruded; however, it pops up significantly. The product is highly porous. When trying to extrude the mixture with the die plate, the extruder blocks.

EXHIBIT 4

Experimental Report

1. Extruder:

A Leistritz ZSE 27 HP 32 D extruder was used. It is a co-rotating twin screw extruder:



2. Extruded Mixture

The following mixture was used in the extruder experiments (see also Experiment 1 of WO 92/15285):

potato starch	810 g
hydrogenated triglyceride	10 g
soya lecithin	5 g
TiO ₂	5 g
Water	17.00 %

3. Experiments

The above mixture was extruded under 4 different parameter conditions (see below Table 1):

	Barrel Temperature Profil
Experiment 1	80°C – 80°C – 80°C
Experiment 2	80°C – 120°C – 120°C
Experiment 3	80°C – 140°C – 140°C
Experiment 4	80°C – 160°C – 120°C

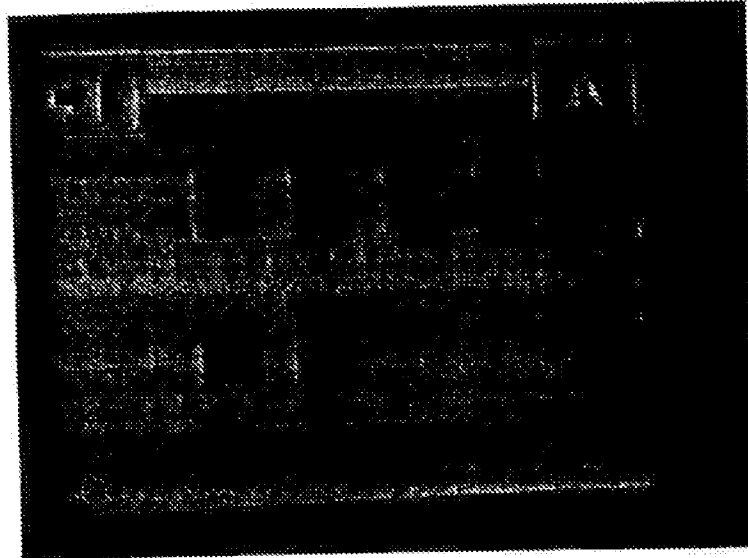
The screw speed was 75 rpm/min.
A round nozzle of 5 mm diameter was used.

- The temperature profile of Experiment 1 conforms with the teaching of the present invention.
- The temperature profiles of Experiments 2 to 4 stepwise approach the conditions as set forth in Experiment 1 of WO 92/15285 in combination with US 4,673,438 (see page 28, lines 5 to 30 of WO 92/15285).

4. Results

4.1 Experiment 1

Online monitor shot:



Product appearance:



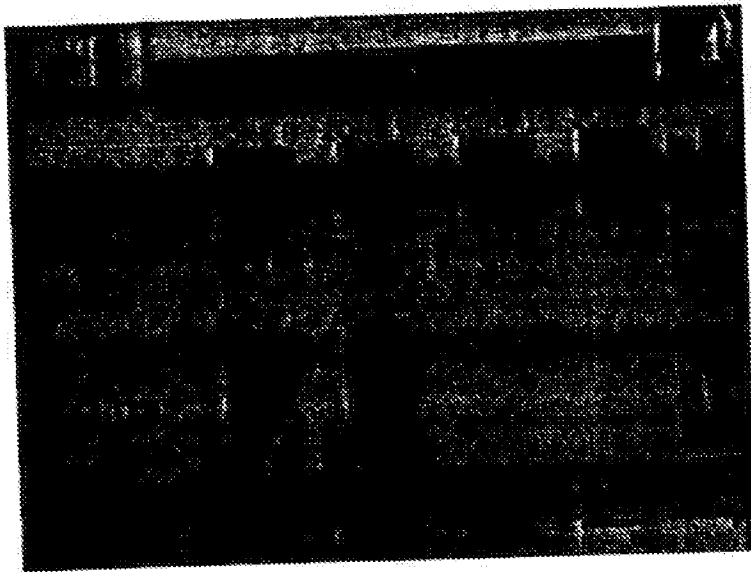
Electron microscopy picture of fracture surface:



The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 85°C.

4.2 Experiment 2

Online monitor shot:



Product appearance:



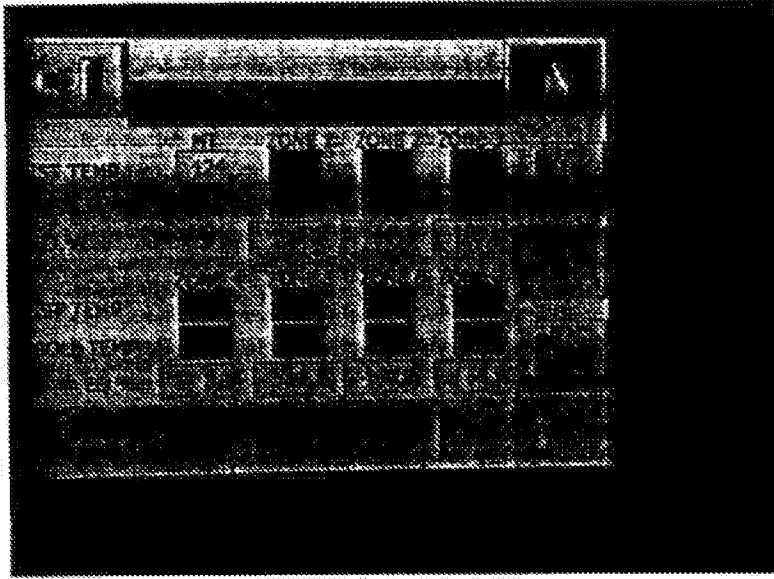
Electron microscopy picture of fracture surface:



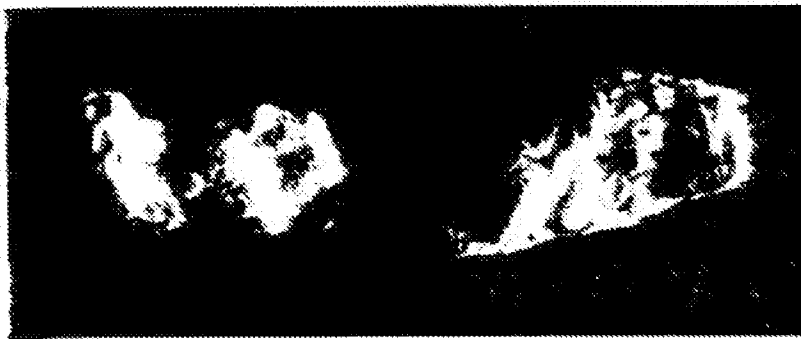
The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 77°C.

4.3 Experiment 3

Online monitor shot:



Product appearance:



Electron microscopy picture of fracture surface:

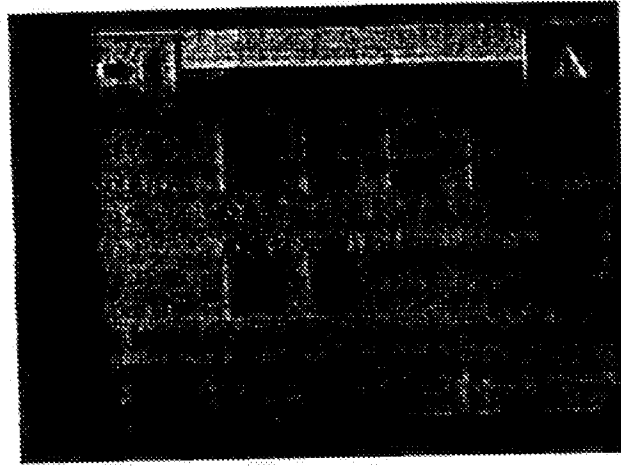


The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 75°C.

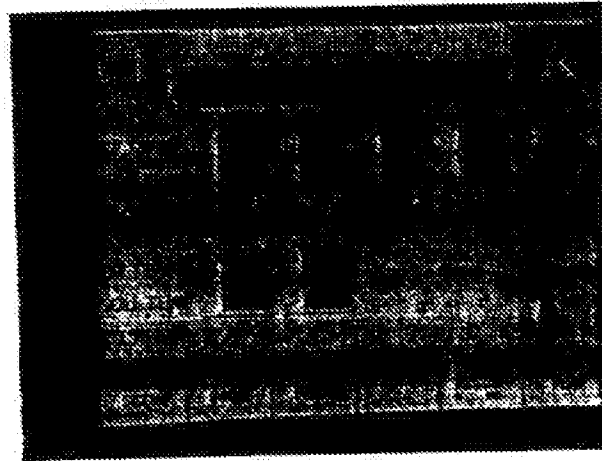
4.4 Experiment 4

Online monitor shots:

When starting the extruder, water vapor leaves the nozzle under high pressure:



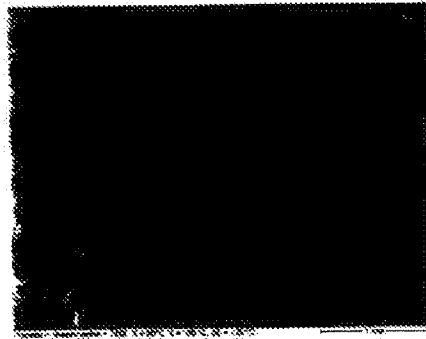
The extrusion process can not be controlled. A foam is formed.



Product appearance:



Electron microscopy picture of fracture surface:



The glass transition temperature was determined using Hyper-Differential Scanning Microscopy and found to be 67°C.